Caption: COVID-19

Title: COVID-19: biological factors in men's vulnerability

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## Introduction

As COVID-19 wreaks havoc across the globe, the UK has been particularly hard hit. The current death toll [up to 1st May 2020] stands at 36 110 across Great Britain, of which 20 373 are male and 15 737 are female [see Figure 1]. This disparity in male mortality has been noted elsewhere,[1–4] and was also recognised during the two previous significant outbreaks of coronavirus: the 2003 Severe Acute Respiratory Syndrome [SARS-CoV] [5,6] and the 2012 Middle East Respiratory Syndrome [MERS]. [7] In particular, during the SARS-CoV outbreak men had a higher case fatality rate of 21.9% as compared to 13.2% for females, and twice as many male-to-female deaths in the 0–44 year age range.[5]

It is too soon for certainty as to why men are more at risk, but our knowledge of the biological, behavioural and socio-cultural factors involved is growing and the picture is getting clearer. This paper will focus onto what is currently understood about the biological implications of being male on the course of the disease.

### Picture COVID-19 binding to an angiotensin converting enzyme 2 (ACE2) receptor

As well as gender, age is seen to be one of the most important risk factors for developing severe disease and a higher mortality,[8] with the median age of those admitted to hospital being 72 years.[9] The most common recorded comorbidities for admission to hospital across the UK are chronic cardiac disease [29%], diabetes [19%], chronic pulmonary disease excluding asthma [19%], and asthma [14%]. Just under half [47%] of patients had no documented comorbidity.[9]

In other studies, those with obesity, cardiovascular disease [especially hypertension and heart failure], diabetes mellitus, respiratory disease, renal and liver disease were found to be the biggest factors in developing the more serious form of the disease and mortality. [10–12] Patients who are immunosuppressed or having had recent surgery are also recognised as being at risk, but this may be due to contact within the hospital setting.[11] In a New York analysis of patients with severe disease, hypertension, obesity and diabetes were found to be the most common factors for admission to hospital.[12] For all these chronic diseases there are a higher proportion of affected men, with a greater number affected at an earlier age. [13]

### Angiotensin converting enzyme 2 [ACE2]

The angiotensin converting enzyme 2 [ACE2] is the main route the virus takes to get into cells,[14] and this is more highly expressed in males.[15] ACE2 is present in the lungs; the blood vessels, the renal tubular cells; the stomach and intestines;

endothelial and smooth muscle cells in the human brain; and the Leydig and Sertoli cells in the seminiferous ducts in the testis. It is more highly expressed in smokers and in obese patients.

The ACE2 receptor is part of the Renin Angiotensin Aldosterone System [RAAS], converting Angiotensin II into Angiotensin (1-7) via its binding to the Mas receptor. Angiotensin II is vasoconstrictive, pro-inflammatory and pro-coagulation - as well having a role in increasing blood pressure. Angiotensin (1-7), on the other hand, is vasodilatory, anti-inflammatory and has a role in glucose homeostasis, lipid metabolism, and energy balance and is both cardio-protective and neuro-protective and has a positive effect in reducing lung injury and kidney pathology. [16–18] The interaction between the virus and ACE2 leaves it depleted through receptor endocytosis and, therefore, leaves the damaging Angiotensin II unopposed, meaning that the body loses the positive effects of Angiotensin (1-7).[14] Losing the metabolic effect of Angiotensin (1-7) may also explain why both obese patients and those with diabetes are at greater risk. A link has also been made with the metabolic syndrome, which is more common in males, and the severity of the disease. [19]

The ACE2 is produced by the X-chromosome, and as females have two X-chromosomes they have twice the capacity to form the enzyme and tend to also create two types of the ACE2. As males only have one X-chromosome, they also have only one form of ACE2. This means that if the virus can unlock the single form of male ACE2 it has access to every cell in which the enzyme is present, while in women the virus has to unlock both of the two forms of ACE2 [one from each X-chromosome] to have the same impact. The effect of this on males is two-fold: it means that the higher ACE2 levels in males may make it easier to get the infection; and once they are infected they may have less ACE2 and therefore Angiotensin (1-7) available to help counter the damaging effects of Angiotensin II. For females there may be less virus entry into the cells, and also more remaining unaffected cells and Angiotensin (1-7) to tackle subsequent lung injury.

**Figure 1. Deaths attributed to COVID-19 infection in Great Britain, distributed by age and sex 19 June 2020.©statista.com**

The availability of the ACE2 is also affected by age, with highest levels found in the younger age patients, which would appear counterintuitive in relation to infection rates and severity of the disease in older age patients. However, as the young are less likely to have other risk factors [such as chronic diseases and comorbidities] they may be more able to use its protective function to fight the disease. In older age patients, a reduced ACE2 may mean the enzyme is more quickly exhausted, leading to the risk of more severe disease.

The ACE2 is also highly expressed within the testis and the prostate,[15] with orchitis, infertility and testicular tumour identified in the earlier SARS-CoV outbreak.[6] The longer term impact of this ACE2 prevalence in male-specific organs should be assessed through the current outbreak.[22,23] It has also been postulated that the virus may be transmissible in seminal fluid.[22]

**Endothelial dysfunction**

Endothelial dysfunction is an important risk factor for cardiovascular disease [CVD], and is of course frequently present in men with erectile dysfunction and Type 2 diabetes. [20]  It appears the SARS-CoV-2 infection facilitates the induction of endotheliitis in multiple organs and the induction of apoptosis might play an important role in endothelial cell injury in these patients. From the practical viewpoint, using drugs that improve endothelial function, such as PDE5i's ACE inhibitors and statins, could be very important in these patients, although many of the vulnerable patients will already be on these drugs because of pre-existing endothelial dysfunction and its known association with male sex and vascular risk factors.

**Coagulopathy**

In addition, the vascular immunopathology associated with COVID-19 presents as a diffuse pulmonary intravascular coagulopathy, which in its early stages is distinct from disseminated intravascular coagulation. Increased circulating D-dimer concentrations caused by pulmonary vascular bed thrombosis with resultant fibrinolysis and elevated cardiac enzyme concentrations in the face of normal fibrinogen and platelet levels are key early features of severe pulmonary intravascular coagulopathy related to COVID-19. Extensive immunothrombosis over a wide pulmonary vascular territory before the confirmation of early COVID-19 viraemia possibly explains the adverse impact of male sex, hypertension, obesity, and diabetes on the prognosis of patients with COVID-19. The combination of immunomodulatory and anticoagulant strategies in patients with high D-dimer concentrations and evidence of myocardial stress requires urgent research. [21]

**Cytokine proteins**

The immune system is also supported by the cytokine proteins, which act as a communicator between cells. They are involved in the pro-inflammatory process, with some [CCL2, CCL3, CCL4 and CCL16] having a protective effect and being found more often in women. Although men to tend to have more of the interleukin cytokines [IL6ST, IL-7, IL-16 and IL-18] that provoke more of an inflammatory response and, with excess stimulation, can lead to the cytokine release syndrome [or cytokine storm] that can rapidly overtake the immune system of the body and result in a catastrophic shock. Men also tend to have more highly expressed TNFSF13b [BAFF], which is associated with an increased risk of inflammation and is associated with the progression of chronic obstructive pulmonary disease [COPD].[15]

**FURIN & TMPRSS2**

For the virus to get into the cells they also need two spike proteins [FURIN & TMRPSS2], with FURIN more highly expressed in the lungs of smokers [with men being more prevalent smokers] and TMPRSS2 is an androgen-responsive gene and more responsive to testosterone and dihydrotestosterone.[24] The modulation of transmembrane protease, serine 2 (TMPRSS2) expression by testosterone has been suggested to contribute to male predominance of COVID-19 infection. [25] This is because the androgen receptor activates the transcription of TMPRSS2 enhancing the transmissibility of COVID-19 infection [26] and because TMPRSS2 are expressed also at pulmonary level, the use of TMPRSS2 inhibitors, and

antiandrogens are being investigated to modulate COVID-19 infections and treat COVID-19 pneumonia, and we await preliminary results. [27,28]

**Wider immunity factors**

Females also have higher expression of TLR7 and TLR8, both of which are important in immune responses and found [and remain active] on both of the X-chromosome, whereas in men there is just a single copy. As such, females are more likely to activate a successful immune response and have been suggested to be more active with single strand viruses such as SARS-CoV-2.[29]

A hormonal component is also at play, with oestrogen having an immuno-protective function by the regulation of myeloid cells and innate lymphocytes and in dampening the proinflammatory cytokines. It may also have a more direct effect on the metabolic function of the cell limiting viral replication. Oestrogen also promotes type 2 repair responses of alveolar macrophages and resolution of the immune response to the virus. In contrast, testosterone tend to have an immune-suppressive effect, by promoting the proinflammatory cytokines and suppressing inflammation.[6,30] Age may therefore have an effect on the viral infection, with oestrogen levels falling in women quickly in the perimenopause whereas testosterone levels remain stable in 75% of men into old age, but this does leave a significant number of men testosterone and oestrogen deficient. [31] Risk factors for a low testosterone include type 2 diabetes, central obesity, erectile dysfunction, sleep apnoea, co-morbidity and others.[32] Female patients are able to achieve viral clearance significantly earlier than males, this may be because the testes was shown to be one of the highest sites of ACE2 expression in 3 independent RNA expression databases [Human Protein Atlas, FAMTOM5 and GETx]. ACE2 was also determined to be highly expressed in testicular cells at the protein levels. In contrast very little expression of ACE2 was seen in ovarian tissue.  High expression of ACE2 in testes raises the possibility that testicular viral reservoirs may play a role in viral persistence in males [33].

Serum testosterone levels may be adversely affected by the testicular involvement and have a significant impact on recovery.[34]. Testosterone may also be helpful by downregulating inflammation. Testosterone deficiency [TD] is associated with increased pro-inflammatory cytokines and testosterone treatment reduces IL-1β, IL-6, and TNF-α [35] A pro-inflammatory state and decline in testosterone has been demonstrated in aging men [36] and those with vascular disease. [37] In theory testosterone may have a role in the events leading to progression of COVID-19 infection and the cytokine storm. Suppression of ACE2 expression by inflammatory cytokines accompanied by the decrease of androgen and oestrogen in some ageing men, may establish a negative correlation between ACE2 expression and COVID-19 mortality. [26] Testosterone levels should be investigated in these men affected by COVID-19 because of the known adverse impact of testosterone deficiency on cardiovascular mortality and heart failure, and men with a low testosterone may be at high risk if they become infected [38].

Conclusion

We are not at the end of the pandemic, and there will be many more theories emerging as to the biological causes and consequences of the disease as our understanding develops. As the search for a vaccination continues apace there are many avenues being followed that may lead to a breakthrough, but this is proving to be a very tricky infection with many twists and turns in the experiences of patients. We fear we are just at the beginning…

Declaration of interests: none declared.

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Picture COVID-19 binding to an angiotensin converting enzyme 2 (ACE2) receptor

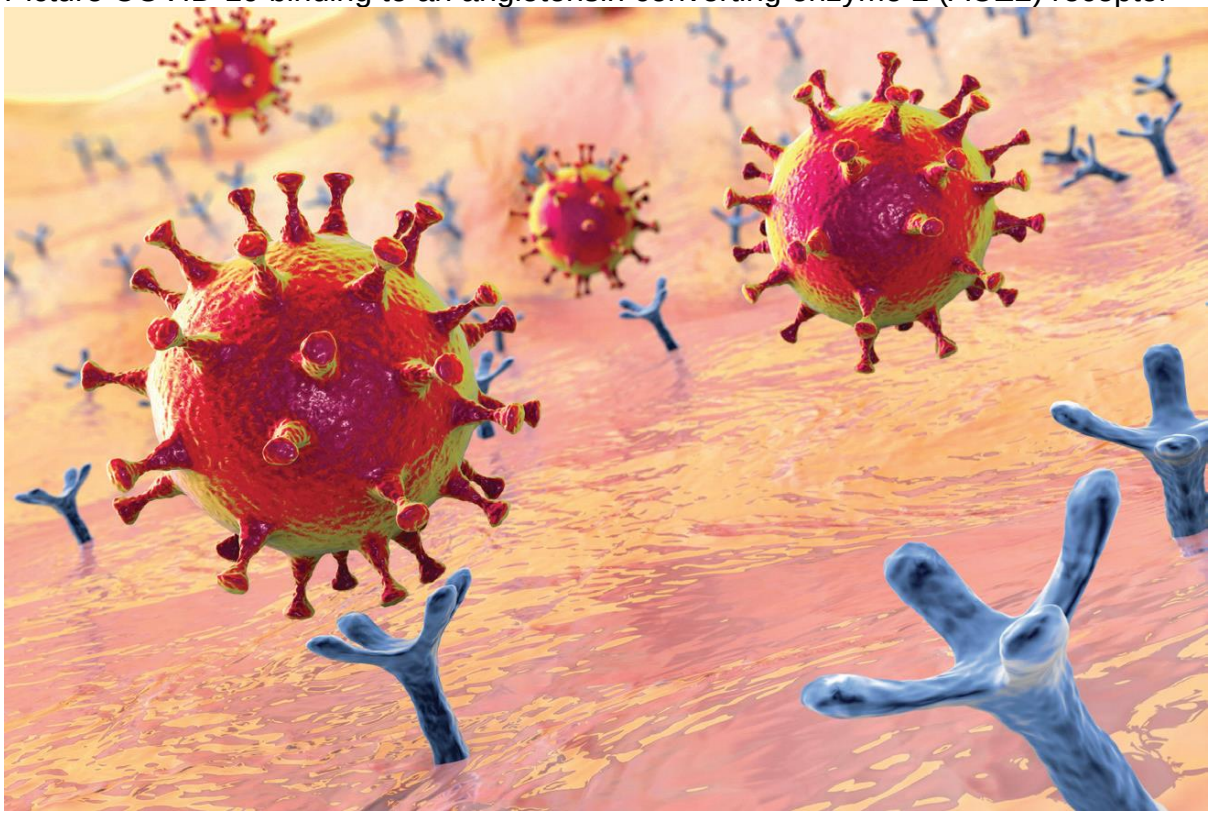

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Figure 1. Deaths attributed to COVID-19 infection in Great Britain, distributed by age and sex 19 June 2020.©statista.com

| Patient age group | Male | Female |
|---|---|---|

| | | |
|---|---|---|
| Under 1 year | 2 | 0 |
| 1 to 14 years | 2 | 2 |
| 15 to 44 years | 325 | 206 |
| 45 to 64 years | 3104 | 1634 |
| 65 to 74 years | 4740 | 2542 |
| 75 to 84 years | 9446 | 6516 |
| 85 years and over | 9566 | 11286 |